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Prebiotic Chemistry in Nanoconfinement

Daniel Muñoz-Santiburcio and Dominik Marx

Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, 44780 Bochum, Germany
E-mail: {*daniel.munoz, dominik.marx*}*@theochem.rub.de*

Water presents extremely different properties depending not only on conditions like temperature and pressure but also on the local environment (bulk vs. interfacial water), which in turn profoundly affects chemical reactions in solution. Here, we present the results of extensive *ab initio* molecular dynamics and metadynamics simulations in which we study some properties of nanoconfined water in mackinawite and a whole pathway for prebiotic peptide synthesis *via* glycine and COS condensation. It is shown that the special chemistry observed in this system is the result of the interplay between the steric and entropic effects intrinsic to nanoconfinement and the different dielectric properties of nanoconfined water compared to the bulk. The results show that prebiotic peptide bond formation is enhanced in nanoconfined water, while peptide hydrolysis is hindered, thus making this environment highly suitable for prebiotic polypeptide synthesis.

1 Introduction

The emergence of life is of special interest for mankind. Even though great advances in science and technology have been achieved, the answer to this fundamental question remains to be found. Various ideas have been developed and innovative experiments have been performed to explain how organic molecules might have been synthesised in a prebiotic "inorganic" environment, and how they organised themselves to form biomolecules of contemporary complexity[1,2]. A two–dimensional scenario like the mineral surface is now considered to be a possible prebiotic stage where such reactions had taken place[3,4]. One of the most acclaimed hypotheses in this respect is that suggested by Wächtershäuser[5,6].

Wächtershäuser proposes a chemo-autotrophic origin of life[5,6], which has been called the "Iron–Sulfur–World" (ISW) scenario. The main assumption in the ISW scenario is that prebiotic reactions like condensations of amino acids are catalyzed by iron–sulfur minerals located near deep sea hydrothermal vents[7,8], i.e. in a high temperature and high pressure environment. Several experimental studies provide support for a possible ISW scenario[9–12] as well as offer mechanistic insight into the peptide polymerisation[13]. Up to now, our computations on JUQUEEN (and previously on JUGENE and even on JUBL, being the first Blue Gene platform in Germany)[14] have identified very important mechanistic and energetic details of peptide synthesis reactions and thus the underlying "Iron–Sulfur–World" origin of life scenario. We have already established that extreme thermodynamic conditions have a dramatic impact on both mechanisms and energetics for prebiotic peptide synthesis[15–17], due to the change of the dielectric properties of water upon rising temperature and pressure, which makes it essentially a different solvent when compared to water at ambient conditions. Now, we determine the impact of nanoconfinement on chemical reactions in solution, which is of utmost importance for prebiotic chemistry. It has been found that an important iron/sulfur precipitate, namely mackinawite, can be produced at hydrothermal vents under ISW conditions[7,18]. This mineral presents a layered structure, and its loosely bonded FeS sheets can be intercalated by water thus obtaining a nanocon-

fined water lamella between FeS plates. Taking into account that the dielectric properties of interfacial water are remarkably different from those of bulk water[19], nanoconfined water (being purely interfacial water) reveals itself as a new and different medium for chemical synthesis as we will show in the following.

2 Nanoconfined Water in Mackinawite

We designed a model system consisting of two $Fe_{32}S_{32}$ mackinawite layers that are intercalated by either 32 or 49 H_2O molecules, being these our setups for "extreme" and "moderately" nanoconfined water (Fig. 1), respectively.

Our *ab initio* simulations of nanoconfined water[20] showed that, while extremely nanoconfined water in mackinawite is "arrested water" and the diffusivity is too low to consider it a suitable medium for chemical synthesis, moderately nanoconfined water presents liquid-like properties and is thus a good medium for prebiotic peptide synthesis. Further *ab initio* simulations in which we studied the excess proton in nanoconfined water[21] revealed most efficient proton transfer. As in bulk water, the excess proton can be considered as a fluxional charge defect even at extreme confinement, being fully incorporated into the hydrogen bond network as a topological defect. The transfer of this excess proton along the hydrogen bond network occurs through the well-known Grotthuss mechanism (Fig. 2) and it is an almost barrierless process, which implies most efficient proton migration even at extreme nanoconfinement conditions.

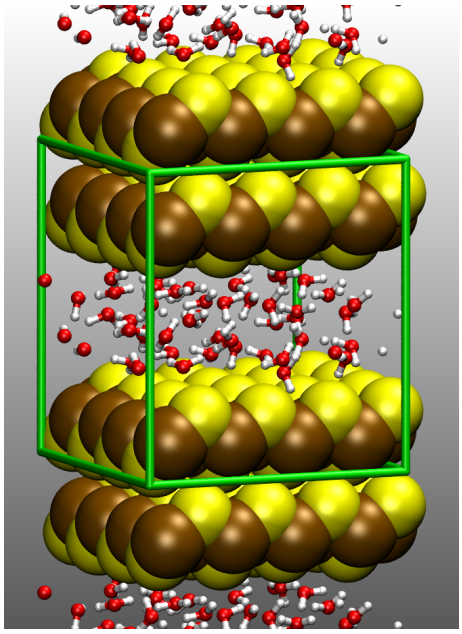

Figure 1. Model system for "moderately nanoconfined" water in mackinawite. Fe atoms are show as brown spheres, S as yellow spheres, and H_2O molecules as balls-and-sticks. The edges of the simulation box are shown in green, and the periodic images along the z axis are also displayed.

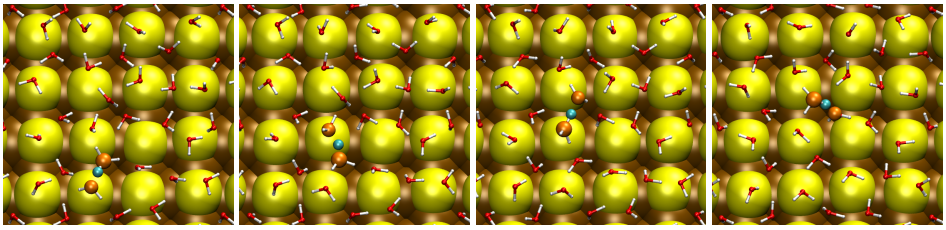

Figure 2. Transfer of an excess proton in "extremely nanoconfined" water by the Grotthuss mechanism. The excess proton is depicted in cyan and the oxygen atoms between which the transfer takes place are depicted in orange.

Our findings not only suggest that, indeed, thin water films confined by such mineral sheets are efficient nanoreactors for prebiotic reactions in Nature, but they might also lead to the design of improved setups for fuel cell membranes.

3 Peptide Synthesis in Nanoconfined Water

In previous stages of the long-term project "*In Silico* Exploration of Possible Routes to Prebiotic Peptide Synthesis by *Ab Initio* Metadynamics", we simulated full peptide synthesis *via* N-carboxyanhydride (NCA) activation at three different thermodynamic conditions (see Fig. 3): ambient bulk water at 300 K and 0.1 MPa (ABW), hot–pressurised bulk water at 500 K and 20 MPa (HPW), and water at an iron-sulfur mineral interface at 500 K

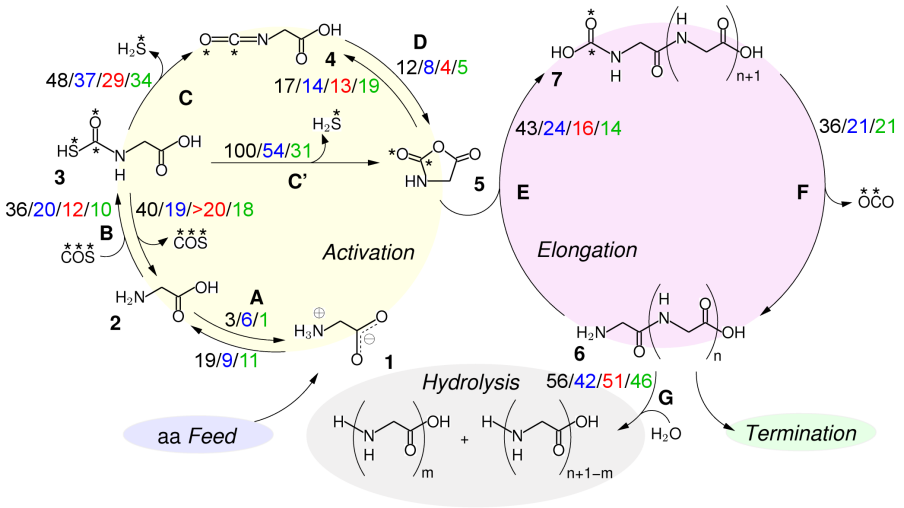

Figure 3. The peptide synthesis route comprising activation, elongation and hydrolysis. The calculated free energy barriers for individual steps of the mechanism are colour-coded; black: ambient bulk water, blue: hot–pressurised bulk water, red: pyrite–water interface at extreme conditions, green: nanoconfined hot–pressurised water in mackinawite; energies are given in $k_{\mathrm{B}}T$ units.

and 20 MPa. Based on free energy calculations and dissecting the detailed reaction mechanisms, our previous studies have concluded the importance of extreme conditions and mineral surfaces for the primordial peptide synthesis[15–17,22]. Moreover, these calculations have identified activation pathways of an amino acid.

The situation of a growing pyrite surface was simulated by surface defects at the interface to the bulk water. Hydrothermally-formed iron sulphide chimneys that are nowadays found at volcanic vents consist of mostly pyrite (FeS_2). However, it is assumed that pyrite is a reaction product in the sense that it precipitated as the monosulphide (FeS) mackinawite[7,18]. As exposed before, being a layered structure it is conceivable that water can enter easily at high pressure and temperature conditions thus producing water/FeS interfaces in a local "lamella geometry" resulting into confinement. Incidentally, there are other layered minerals capable of hosting such water lamellae in their interlayer space, some of which like fougèrite (or "green rust") may be of paramount importance for prebiotic chemistry as they have been proposed as part of a primordial pyro-phosphate synthetase nanoengine[23]. Taking up these thoughts, we carried out the investigation of the prebiotic peptide cycle in nanoconfined hot–pressurised water (500 K and 20 MPa, NCW). Our simulations reveal remarkable differences in energetics and mechanisms compared to bulk water. These can be traced back to a unique combination of factors, namely the different dielectric properties of interfacial water w.r.t. the bulk[19] as well as entropic and steric factors intrinsic to nanoconfinement which make nanoconfined water a whole new medium for chemical synthesis.

The way in which extreme conditions influences the reactions comprising the peptide cycle had been successfully studied by us in previous periods of this project[15–17]. It is well established that the dielectric constant of water is remarkably reduced[24] when raising temperature and pressure from ambient to extreme conditions. This reduction is by more than a factor of two in our previously studied cases (from $\epsilon \approx 80$ at AMB to $\epsilon \approx 32$ in HPW)[24,25], thus essentially making HPW another solvent than at ambient conditions. In consequence, charged species are much favoured in ambient conditions, while extreme conditions discourage the formation of these and stabilise the neutral form of reactants and intermediates. In stark contrast to what is observed in the limit of bulk solvation, our recent results show that charged species are again stabilised in NCW. This can be explained with an increase in the dielectric constant of water in nanoconfinement w.r.t. the bulk. It has been shown that the parallel component of the dielectric tensor in interfacial water is higher in the interfacial region than in the bulk-like region.[26,19]. This higher dielectric constant of interfacial compared to bulk water is responsible for the lower relative free energy of charged species and transition states in NCW compared to HPW. This is clearly realised in the zwitterionic equilibrium of glycine (reaction **A** in Fig. 3): while the neutral form was stabilised in HPW compared to AMB conditions, in NCW the equilibrium is again displaced towards the zwitterionic form (Fig. 4). In some other reactions of the peptide cycle, this stabilisation of charged species results in changes of the reaction mechanism: from concerted in HPW to stepwise in NCW. Such is the case in reaction steps **C'** (Fig. 5) or **D** (Fig. 6), which in NCW proceed *via* the charged intermediates **3.2** and **4.1**, respectively, while these intermediates are only transition states in HPW.

In addition to this change in the dielectric properties of water, other factors determine the chemistry observed in the nanoconfined water lamella. These are mainly steric and entropic in nature: while addition (like **B** or **E**) or cyclisation reactions (like **C'** or **D**) are

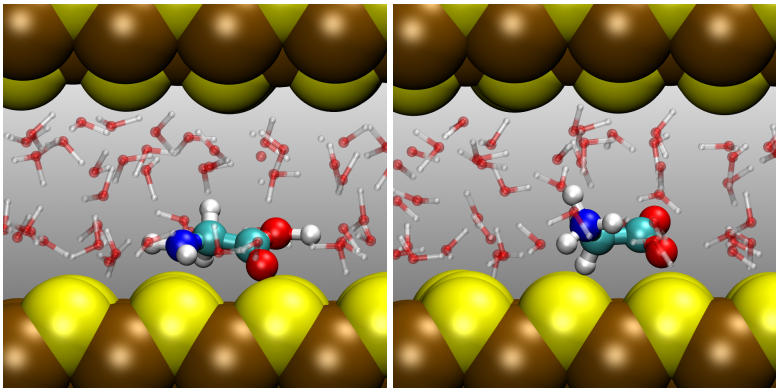

Figure 4. Snapshots for the reaction step **A** (protonation equilibrium of glycine). In nanoconfined hot–pressurised water, the neutral form of glycine (left) is much less stable than the zwitterionic form (right), just like in bulk, ambient water; while in bulk hot–pressurised water the neutral form is stabilised compared to those two conditions.

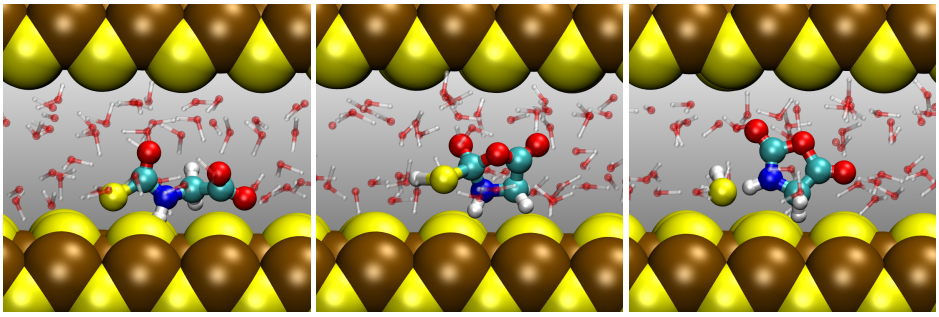

Figure 5. Snapshots for the reaction step **C**. From left to right: Carbamate **3**, charged intermediate **3.2** and SH^- + isocyanate **4**.

quite facilitated compared to HPW, elimination reactions are not quite affected. For addition reactions, the reduction in accessible space intrinsic to nanoconfinement limits the diffusive modes, forcing the reactants to have more reactive encounters; while for cyclisations it discourages stretched conformations and favours compact foldings which results in intramolecular bond formation. On the contrary, elimination reactions do not benefit from this reduced size of the reaction chamber, thus being less affected by nanoconfinement.

In the special case of the peptide hydrolysis reaction, the peptide bond is protected against water attack thanks to the sterical hindrance provided by the confining mackinawite sheets and the side chains of the dipeptide. This renders peptide hydrolysis unfavoured in NCW when compared to AMB or HPW conditions, while peptide elongation is not penalised as it involves the reaction of the terminal amino group of the dipeptide with a compact NCA molecule, which should not suffer as much steric hindrance as the water attack on the less accessible peptide bond. Because of this, polypeptide formation should be facilitated in nanoconfinement in comparison with bulk water. The implications of this

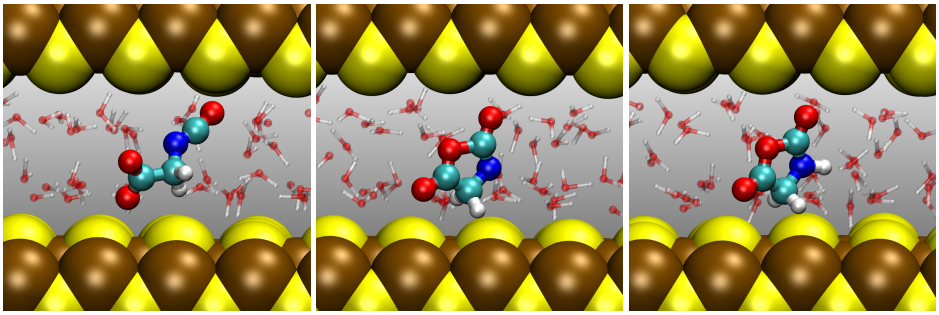

Figure 6. Snapshots for the reaction step **D**. From left to right: Isocyanate **4**, charged intermediate **4.1** and N-carboxyanhydride **5**.

result can be quite deep as it supports some hypotheses: it has been proposed that layered minerals like mackinawite could have acted as inorganic templates for the formation of peptide α-sheets or amyloids, which after incorporating metal atoms or inorganic clusters could have become protoenzymes[23].

4 Outlook

As we have exposed, the subtle interplay between the peculiar properties of nanoconfined water and the steric and entropic factors intrinsic to nanoconfinement determines the very special chemistry observed in such systems. From this starting point, new paths are now open for future lines of research: first, the nature of the reactants may have a great influence on the reactions, since for instance the hydrophobic/hydrophilic character of the aminoacid residues will impose different arrangements of the solvating waters, which is very likely to have a deep impact on both mechanisms and energetics. Second, these findings can be generalised to other systems capable of hosting such nanoconfined water lamellae like green rusts[23], and it would be of great interest to observe how the specific confining surface affects the reactions taking place therein. Finally, nanoconfined water is ubiquitous in biological systems, as it can be found in the crowded regions inside cells or in water pockets and tunnels in biological macromolecules[27]. Hence, we expect that the study of the distinct properties of nanoconfined water will result not only in unravelling several yet poorly understood phenomena, but also in new and exciting applications for chemistry, biology and materials science.

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References

1. I. Fry, *The Emergence of Life on Earth: A Historical and Scientific Overview*, Rutgers University Press, New Jersey, U.S.A., 2000.
2. P. L. Luisi, *The Emergence of Life from Chemical Origins to Synthetic Biology*, Cambride University Press, Cambride, UK, 2006.
3. M. Schoonen, A. Smirnov, and C. Cohn, *A Perspective on the Role of Minerals in Prebiotic Synthesis*, Ambio, **33**, 539, 2004.
4. S. Leach, I. W. M. Smith, and C. S. Cockell, *Introduction: conditions for the emergence of life on the early Earth (Royal SocietyDiscussion Meeting Issue)*, Phil. Trans. R. Soc. B, **361**, 1675–1679, 2006.
5. G. Wächtershäuser, *Before enzymes and templates: theory of surface metabolism*, Microbiol. Rev., **52**, 452, 1988.
6. G. Wächtershäuser, *Groundworks for an evolutionary biochemistry: the iron-sulphur world*, Prog. Biophys. Mol. Biol., **58**, 85–201, 1992.
7. W. Martin and M. J. Russell, *On the origins of cells: a hypothesis for the evolutionary transitions from abiotic geochemistry tochemoautotrophic prokaryotes, and from prokaryotes*, Phil. Trans. R. Soc. Lond. B., **358**, 59–85, 2003.
8. S. C. Singh, W. C. Crawford, H. Carton, T. Seher, V. Combier, M. Cannatand, J. P. Canales, D. Düsünür, J. Escartin, and J. M. Miranda, *Discovery of a magma chamber and faults beneath a Mid-Atlantic Ridge hydrothermal field*, Nature, **442**, 1029–1032, 2006.
9. C. Huber and G. Wächtershäuser, *Activated Acetic Acid by Carbon Fixation on (Fe,Ni)S Under Primordial Conditions*, Science, **276**, 245, 1997.
10. C. Huber and G. Wächtershäuser, *Peptides by Activation of Amino Acids with CO on (Ni,Fe)S Surfaces: Implications for the Origin of Life*, Science, **281**, 670–672, 1998.
11. C. Huber, W. Eisenreich, S. Hecht, and G. Wächtershäuser, *A Possible Primordial Peptide Cycle*, Science, **301**, 938–940, 2003.
12. L. Leman, L. Orgel, and M. R. Ghadiri, *Carbonyl Sulfide–Mediated Prebiotic Formation of Peptides*, Science, **306**, 283–286, 2004.
13. H. R. Kricheldorf, *Polypeptides and 100 Years of Chemistry of α-Amino Acid N-Carboxyanhydrides*, Angew. Chem. Int. Ed., **45**, 5752–5784, 2006.
14. N. N. Nair, E. Schreiner, and D. Marx, *Prebiotic Peptide Synthesis on Blue Gene Platforms at "Iron-Sulfur-World" Conditions*, inSiDE, **6**, 30–35, 2008, See: `http://inside.hlrs.de/_old/htm/Edition_02_08/article_09.html` (accessed on August 25, 2015).
15. E. Schreiner, N. N. Nair, and D. Marx, *Influence of extreme thermodynamic conditions and pyrite surfaces on peptide synthesis in aqueous media*, J. Am. Chem. Soc., **130**, no. 9, 2768–2770, 2008.
16. N. N. Nair, E. Schreiner, and D. Marx, *Peptide synthesis in aqueous environments: The role of extreme conditions on amino acid activation*, J. Am. Chem. Soc., **130**, no. 43, 14148–14160, 2008.
17. E. Schreiner, N. N. Nair, and D. Marx, *Peptide Synthesis in Aqueous Environments: The Role of Extreme Conditions on Peptide Bond Formation and Peptide Hydrolysis*, J. Am. Chem. Soc., **131**, no. 38, 13668–13675, 2009.

18. M. J. Russell and A. J. Hall, *The emergence of life from iron monosulphide bubbles at a submarine hydrothermal redox and pH front*, J. Geolog. Soc., **154**, 377–402, 1997.
19. D. J. Bonthuis, S. Gekle, and R. R. Netz, *Dielectric profile of interfacial water and its effect on double-layer capacitance*, Phys. Rev. Lett., **107**, no. 16, 166102, 2011.
20. C. Wittekindt and D. Marx, *Water confined between sheets of mackinawite FeS minerals*, J. Chem. Phys., **137**, no. 5, 054710, 2012.
21. D. Muñoz-Santiburcio, C. Wittekindt, and D. Marx, *Nanoconfinement effects on hydrated excess protons in layered materials*, Nat. Commun., **4**, 2349, Aug 2013.
22. E. Schreiner, N. N. Nair, C. Wittekindt, and D. Marx, *Peptide synthesis in aqueous environments: the role of extreme conditions and pyrite mineral surfaces on formation and hydrolysis of peptides*, J. Am. Chem. Soc., **133**, no. 21, 8216–8226, 2011.
23. M. J. Russell, L. M. Barge, R. Bhartia, D. Bocanegra, P. J. Bracher, E. Branscomb, R. Kidd, S. McGlynn, D. H. Meier, W. Nitschke, et al., *The drive to life on wet and icy worlds*, Astrobiology, **14**, no. 4, 308–343, 2014.
24. H. Weingärtner and E. U. Franck, *Supercritical water as a solvent*, Angew. Chem., Int. Ed., **44**, no. 18, 2672–2692, 2005.
25. M. Uematsu and E. U. Frank, *Static dielectric constant of water and steam*, J. Phys. Chem. Ref. Data, **9**, no. 4, 1291–1306, 1980.
26. V. Ballenegger and J.-P. Hansen, *Dielectric permittivity profiles of confined polar fluids*, J. Chem. Phys., **122**, no. 11, 114711, 2005.
27. D. Lucent, C. D. Snow, C. Aitken Echeverría, and V. S. Pande, *Non-bulk-like solvent behavior in the ribosome exit tunnel*, PLoS Comput. Biol., **6**, no. 10, e1000963, 2010.